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Extended Abstract

Acute lymphoblastic leukemia (ALL) and proteomics: Looking for protein-biomarkers of pediatric relapses

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Abstract

It may be a clich?, but it is nonetheless true: if we all have achieved more, it is because we stand on the shoulders of those early giants. Because of them, the cure of childhood ALL may be the greatest cancer story ever told (By Joseph V. Simone, MD: December 2008 as part of the special ASH anniversary brochure, 50 Years in Hematology: Research that revolutionized patient care. Since 1950, important break throughs in the treatment of pediatric ALL have been achieved. Now a days, more than 80% of children suffering ALL can be cured. However, around 30% of the patients will still relapse, being this group of patients the ones focused by the investigators. We aim to review proteomics research on pediatric ALL due to (a) this tool is providing several important advances to combat cancer cells, (b) when applying phosphoproteomics for leukemia investigation, novel and real protein-biomarkers of resistance or sensitivity to drugs which target the signalling-networks will appear. We detail important tips for a proper phospho-quantitative design and strategy for pediatric ALL (relapse vs. remission) research studies when using human body fluids from cerebrospinal and bone-marrow. A schedule for the analysis of samplesbody fluids according to the different states of the patients is explained. Moreover, important advances on leukemia coupled to proteomics tools are also explained. The final goal is to stimulate pediatric ALL research via proteomics in order to ?build? the reference map of the signalling-networks from leukemic cells at relapse, thus significant clinical and therapy advances for ALL-relapse can be achieved.

Acute lymphoblastic leukaemia (ALL) is the most common malignant disease diagnosed in children and represents one-third of paediatric malignancies. There are still around 30% of the patients to be relapsed, even though therapies for leukaemia have been improved over last decades. Twenty per cent of relapse cases have an isolated extramedullary relapse, of which the central nervous system relapse is about 65% [1]. Three main prognostic factors are considered in the outcome of first ALL-relapse patients, including the time of the initial diagnosis to relapse associated with better prognosis in late relapses, the location of the relapse with better prognosis for extramedullary relapses, and the immunophenotype of the leukemic cells with worse prognosis for T-cell phenotype. Treatment of relapse dependent on those prognostic factors includes chemotherapy and bone marrow transplant in patients with high risk of early and late relapses with poor chemotherapy responses. The characterization of the relapse leukemic blasts at an extramedullary site has been defined via the polymerase chain reaction (PCR) of markers, e.g. immunoglobulins and T-cell receptor gene rearrangements.

PCR-based analysis of minimal residual disease (MRD) is used to detect residual leukemic cells can be detected by during therapy or even single leukemic cell. Emerging technologies have been developed rapidly to enable to detect circulating tumour cells in various cancers [2]. It is essential to accurately predict patients to differentiate risk groups to optimize the strategy, as paediatric ALL is a heterogeneous disease with varied response to treatment. Risk stratification is classified into the standard, low, intermediate, or high, based on molecular and/or cytogenetic markers (e.g. BCR-ABL and MLL-AF4 rearrangements) and responses to treatment. Chromosomal irregularities are frequently involved in non-random chromosomal translocations to produce new gene fusions or cause inappropriate expressions of oncogenes or altered correspondent proteins. Genetic alterations [e.g. t(9;22), t(1;19), t(12;21) and the rearrangement of the MLL gene on chromosome 11q23] have been suggested to impact the prognosis of patients [3–6].

Risk-based therapy is emphasized in therapeutic protocols for paediatric ALL to reduce the toxicity in patients with low risk and provide aggressive therapies for those with high risk. Age, initial white blood cells, ALL subtype, chromosomal aberrations, or MRD have been considered in the risk stratification, although the exact disease-specific and sensitive biomarkers remain unknown [3–11]. Proteomics is an opening and new window to make the discovery and identification of protein-based biomarkers possible in paediatric ALL-relapses, and a useful tool to develop individual and personalized therapies [12]. Enlightenment and complete comprehension of cell-signalling pathways and activation/deactivation are the key for discerning the progression, remission, or relapse of ALL, since cell-signalling pathways regulate and control cell proliferation, differentiation, survival and apoptosis [13].

Signalling pathways are controlled by post-translational modifications (PTMs) via phosphorylation of protein kinases and phosphatases. Functional pathway-mapping methodologies allow direct measurements of the activation/deactivation of proteins in signalling transduction pathways, with a great promise for discovery and identification of altered signalling pathways in ALL cells after the occurrence

of relapse. Proteomics can be used to search new therapeutic targets for drug discovery and development and identify ALL-relapse-specific biomarkers earlier, and develop specific inhibitors for targeted signalling in patients with relapse.

Protein activation/deactivation is hardly analysed directly through gene-expression profiling, since PTMs are not predictable from gene expression. Strategies of phosphoproteomics can be used to profile the activation/deactivation of key molecules in signalling pathways of leukemic cells from ALL patients between stable remission and relapse.

A reference map of activated/deactivated pathways associated with clinical ALL-relapse can be created. Our proposed strategy allows to measure the phosphorylation levels of key signalling proteins and to identify mutated protein-residues at diagnosis, during chemotherapy, or at the end of chemotherapy to complete remission and/or relapse. The strategy can be performed in cerebrospinal-fluid, bone-marrow, or serum, via injection in the mass spectrometer. We have a correct simple sample study design of ALL-relapse for clinical proteomic research to get the 'reference-signalling map' of ALL between remission and relapse.

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